

## CLINICAL SCIENCE

# High cardiorespiratory fitness is more beneficial in pre-diabetic men than women

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**OBJECTIVES:** To investigate gender-specific relationships between cardiorespiratory fitness and factors that predict the development of diabetes and to identify the risk factors that predict fasting plasma glucose and 2-hour plasma glucose levels.

**INTRODUCTION:** Different risk factors (e.g., low cardiorespiratory fitness) may cause elevated plasma glucose levels in men compared to women. Therefore, gender-specific analyses are needed.

**METHODS:** Cardiorespiratory fitness (maximal power output achieved during a standard cycle ergometry test), resting blood pressure, total serum cholesterol, high-density lipoprotein cholesterol and triglyceride levels were measured in 32 pre-diabetic men (mean age:  $57.2 \pm 6.8$  years; mean body mass index (BMI):  $28.5 \pm 3.0$  kg/m<sup>2</sup>) and 40 pre-diabetic women (mean age:  $55.0 \pm 7.3$  years, mean BMI:  $30.4 \pm 5.7$  kg/m<sup>2</sup>). A stepwise regression with backward variable selection was performed to construct models that predict 2-hour and fasting plasma glucose levels.

**RESULTS:** Maximal power output was inversely related to the 2-hour plasma glucose level in the entire group ( $r = -0.237$ ,  $p < 0.05$ ), but this relationship was significant only for males ( $r = -0.404$ ,  $p < 0.05$ ). No significant correlation was found between female gender and cardiorespiratory fitness. Age and cardiorespiratory fitness were significant predictors of 2-hour plasma glucose levels in men. High-density lipoprotein cholesterol was predictive of 2-hour plasma glucose levels in women. Triglycerides in women and BMI in men were the only predictors of fasting plasma glucose levels.

**CONCLUSIONS:** These findings may have consequences for the development of gender-specific diabetes prevention programs. Whereas increasing cardiorespiratory fitness should be a key goal for men, improving the lipid profile seems to be more beneficial for women. However, the present results do not negate the positive effects of increasing cardiorespiratory fitness in women.

**KEYWORDS:** Fitness Level; Impaired Fasting Glucose; Impaired Glucose Tolerance; Gender; Diabetes.

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## INTRODUCTION

In 2000, there were an estimated 151 million cases of type 2 diabetes worldwide. This figure increased to 285 million in 2010, and it is predicted that 438 million people will suffer from diabetes by 2030.<sup>1</sup>

Type 2 diabetes stems from interactions between genetics, behavior and environment. The genetic basis of the disease is still unclear,<sup>2</sup> but there is strong evidence that obesity and inactivity are the main causes of type 2 diabetes.<sup>2-4</sup>

Many previous studies that have investigated the relationship between physical fitness and type 2 diabetes have

had some limitations. One such limitation is the use of self-reported levels of physical activity.<sup>5-9</sup> Self-reporting tends to be imprecise<sup>10</sup> and only correlates moderately with objective measures of cardiorespiratory fitness.<sup>11</sup> Recent studies have overcome this limitation and report that fitness level and diabetes are inversely related.<sup>3,10,12,13</sup>

Most studies have not acknowledged that risk factors for elevated plasma glucose levels are different in men compared to women.<sup>14</sup> Sui et al. found that high physical fitness levels did not eliminate diabetes risk in women,<sup>3</sup> but fitness predicted all-cause mortality among women with impaired fasting glucose (IFG) or undiagnosed diabetes.<sup>15</sup>

The aforementioned studies also did not distinguish between IFG and impaired glucose tolerance (IGT) at baseline. Both IFG and IGT are associated with similar risks for the development of type 2 diabetes,<sup>16,17</sup> but the pathogenic backgrounds and etiologies may be different.<sup>7,18</sup>

The present analysis, as part of a diabetes prevention study,<sup>19</sup> aimed to evaluate gender-specific relationships between measured cardiorespiratory fitness and factors that predict the development of diabetes, as described by Schwarz et al.,<sup>20</sup> in patients with IFG or IGT. Furthermore, the study aimed to identify gender-specific risk factors that predict levels of fasting plasma glucose (FPG) and 2-hour plasma glucose levels (2-h PG) to gain insight into the early stages of the disease's etiology. Based on the findings of Sui et al.,<sup>3</sup> we hypothesized that cardiorespiratory fitness is related to plasma glucose levels in men, but not in women. We also speculated that other differences in diabetes risk factors exist between men and women.

## MATERIALS AND METHODS

### Subjects

General practitioners from western states in Austria were informed about the study and invited to participate. The first ten who agreed to participate were asked to recruit patients (males and females) with IFG and/or IGT primarily through member screening for high-risk groups, such as first-degree relatives of patients with type 2 diabetes and overweight individuals between the ages of 40 and 65 years. IFG was defined as FPG levels  $\geq 100$  mg/dl and  $< 126$  mg/dl, and IGT was defined as 2-h PG values in the oral glucose tolerance test (OGTT) of  $\geq 140$  mg/dl and  $< 200$  mg/dl.<sup>21</sup> Seventy-two sedentary patients (40 female and 32 men) with IFG, IGT or both provided written informed consent to participate. The present analysis was part of a diabetes prevention study.<sup>19</sup> The following exclusion criteria were used: diabetes mellitus, terminal disease with less than 3 years to live, and cardiopulmonary or musculoskeletal diseases not compatible with an exercise program. Baseline characteristics are shown in Table 1. The study protocol was approved by the Ethics Committee of the Medical University of Innsbruck with the report number, AN2458.

### Anthropometric data

Body height was measured without shoes to the nearest 0.5 cm. Body weight was measured with light clothing and without shoes to the nearest 0.1 kg. Body mass index (BMI) was calculated as the ratio of body weight in kilograms to the square of the height in meters ( $\text{kg}/\text{m}^2$ ). Heights and weights were measured by various medical teams using different devices, but all devices were calibrated, and all procedures were standardized. Body fat percentage was measured in 36 participants using body impedance analysis (B.I.A. 2000M, Data Input, Germany).

### Laboratory Assessments

Venous blood samples were obtained in the early morning after overnight fasting and were analyzed for FPG, total serum cholesterol (CHOL), high-density lipoprotein cholesterol (HDL) and triglyceride (TG) levels. We determined 2-h PG during an OGTT using 75 g of glucose dissolved in water. Blood analyses were performed by different laboratories because of the multicenter study design; however, all laboratories met high quality criteria and underwent regular external quality controls.

### Exercise testing

Patients who satisfied the criteria for IFG and/or IGT performed a symptom-limited incremental cycle ergometry

**Table 1 - Baseline characteristics of the participants.**

| Variables                                     | n  | All               | n  | Men                | n  | Women            |
|---|----|-------------------|----|--------------------|----|------------------|
| Age (years)                                   | 72 | 56.0 $\pm$ 7.1    | 32 | 57.2 $\pm$ 6.8     | 40 | 55.0 $\pm$ 7.3   |
| Body weight (kg)                              | 72 | 85.2 $\pm$ 14.8   | 32 | 88.6 $\pm$ 11.8    | 40 | 82.6 $\pm$ 16.6  |
| BF (%)  | 36 | 30.1 $\pm$ 8.6    | 18 | 26.2 $\pm$ 4.5*    | 18 | 34.1 $\pm$ 9.9   |
| Height (cm)                                   | 72 | 170 $\pm$ 8       | 32 | 176 $\pm$ 6*       | 40 | 165 $\pm$ 6      |
| BMI ( $\text{kg}/\text{m}^2$ )                | 72 | 29.6 $\pm$ 4.8    | 32 | 28.5 $\pm$ 3.0     | 40 | 30.4 $\pm$ 5.7   |
| FPG (mg/dl)                                   | 72 | 109.6 $\pm$ 7.5   | 32 | 109.9 $\pm$ 7.9    | 40 | 109.4 $\pm$ 7.3  |
| 2-h PG (mg/dl)                                | 72 | 134.9 $\pm$ 31.7  | 32 | 140.7 $\pm$ 29.6   | 40 | 130.3 $\pm$ 33.1 |
| CHOL (mg/dl)                                  | 72 | 226.6 $\pm$ 36.4  | 32 | 227.4 $\pm$ 43.5   | 40 | 226.0 $\pm$ 30.1 |
| HDL (mg/dl)                                   | 72 | 56.6 $\pm$ 15.2   | 32 | 52.6 $\pm$ 16.7*   | 40 | 59.8 $\pm$ 13.3  |
| TG (mg/dl)                                    | 70 | 177.2 $\pm$ 176.2 | 30 | 240.9 $\pm$ 238.8* | 40 | 129.5 $\pm$ 84.3 |
| BPsys Rest (mmHg)                             | 67 | 128 $\pm$ 16      | 30 | 131 $\pm$ 16       | 37 | 126 $\pm$ 15     |
| BPdia Rest (mmHg)                             | 67 | 88 $\pm$ 13       | 30 | 83 $\pm$ 12*       | 37 | 91 $\pm$ 13      |
| Ppeak (Watt/kg)                               | 72 | 1.6 $\pm$ 0.4     | 32 | 1.8 $\pm$ 0.4*     | 40 | 1.5 $\pm$ 0.4    |
| VO <sub>2</sub> peak (METs) cal <sup>35</sup> | 72 | 7.0 $\pm$ 1.4     | 32 | 7.5 $\pm$ 1.4*     | 40 | 6.7 $\pm$ 1.3    |
| HRpeak (b/min)                                | 72 | 147 $\pm$ 18      | 32 | 144 $\pm$ 17       | 40 | 149 $\pm$ 19     |
| BPsys peak (mmHg)                             | 67 | 195 $\pm$ 27      | 30 | 198 $\pm$ 26       | 37 | 193 $\pm$ 27     |
| BPdia peak (mmHg)                             | 66 | 95 $\pm$ 15       | 30 | 95 $\pm$ 11        | 36 | 95 $\pm$ 18      |
| HR50Watt<br>(%HRpeak)                         | 61 | 70 $\pm$ 12       | 25 | 64 $\pm$ 13*       | 36 | 75 $\pm$ 10      |
| HR100Watt<br>(%HRpeak)                        | 57 | 85 $\pm$ 13       | 24 | 76 $\pm$ 11*       | 33 | 92 $\pm$ 9       |
| La50Watt (mmol/L)                             | 55 | 1.7 $\pm$ 0.7     | 22 | 1.7 $\pm$ 0.6      | 33 | 1.7 $\pm$ 0.8    |
| La100Watt (mmol/L)                            | 49 | 3.0 $\pm$ 1.1     | 19 | 2.5 $\pm$ 0.9*     | 30 | 3.4 $\pm$ 1.1    |

Abbreviations: Body mass index (BMI), body fat (BF), fasting plasma glucose (FPG), 2-hour plasma glucose (2-h PG), total serum cholesterol (CHOL), high-density lipoprotein cholesterol (HDL), triglyceride (TG), systolic blood pressure at rest (BPsys Rest), diastolic blood pressure at rest (BPdia Rest), peak power output (Ppeak), peak heart rate (HRpeak), peak systolic blood pressure (BPsys peak), peak diastolic blood pressure (BPdia peak), maximal oxygen uptake, calculated according to the American College of Sports Medicine<sup>35</sup> (METs), blood lactate concentrations at 50 and 100 watts (La50Watt, La100Watt), heart rate at 50 and 100 watts expressed as a % of the peak heart rate (HR50Watt, HR100Watt). Data are means  $\pm$  SD.

\*denotes significant differences between men and women ( $p < 0.05$ ). For the t-test, ln transformed TG were used.

test to assess cardiorespiratory fitness indicated by the maximal power output achieved. We did not analyze respiratory gases because these devices were not available at all of the laboratories. However, due to the very close correlation between peak power output and maximal oxygen uptake ( $r = 0.97$ ),<sup>22</sup> peak power output can be considered to represent maximal oxygen uptake or maximal aerobic capacity. A detailed description of the test is available in an earlier report.<sup>19</sup> Briefly, blood pressure (BP) and blood lactate concentration (La) were measured after a 5-minute resting period on the cycle ergometer (Ergometrics 900, Ergoline, Germany). Tests were initiated at a workload of 25 watts with an incremental increase of 25 watts every 2 minutes until exhaustion. The pedal rate was held at 70 to 80 rpm. Heart rate was continuously monitored with an electrocardiogram recording, and BP and La (enzymatic method, Biosen 5040, Magdeburg, Germany) were measured at the end of each workload. The test was stopped when subjects were unable to continue because of fatigue (pedaling rate  $< 40$  rpm), dyspnea or pain or when an abnormal ECG or BP value ( $> 240/120$  mmHg) was noticed. Cardiorespiratory fitness was defined as the highest power achieved during the test divided by body weight (Watt/kg).

### Statistics

Unpaired t-tests were used to analyze the differences between men and women. The associations between FPG, 2-h PG levels, CHOL, HDL, TG, BMI and cardiorespiratory

fitness (i.e., relative power, Watt/kg) were calculated using Pearson correlation analyses. A moderate correlation of  $r=0.3$  between plasma glucose levels and cardiorespiratory fitness was considered meaningful. Accordingly, a sample size of 67 provided a power of 80% (one-tailed).

All data, except TG data, were normally distributed (Kolmogorov-Smirnov Test); therefore, ln-transformed TG (lnTG) values were used in all analyses. A stepwise regression with backward variable selection was performed to construct models that predicted 2-h PG and FPG levels. The regression analysis was performed for men and women separately and was initiated with a model that included the risk factors that predict the development of diabetes as described by Schwarz et al.<sup>20</sup> (i.e., age, BMI, HDL, TG, BP, and physical activity). To obtain more accurate information on physical activity, measured cardiorespiratory fitness was used in the analysis instead of self-reported levels of physical activity. The p-value for inclusion in the backward regression model was set at 0.1. For t-tests and correlation analyses, p-values  $<0.05$  were considered to indicate statistical significance. Data are presented as means  $\pm$  standard deviation (SD).

## RESULTS

Measured variables for the entire group and by gender are shown in Table 1. Men had higher TG levels ( $p=0.002$ ), lower percent body fat ( $p=0.005$ ), lower HDL levels ( $p=0.045$ ) and lower resting diastolic BP ( $p=0.011$ ). Cardiorespiratory fitness was higher in men ( $p=0.011$ ). Men had significantly lower La at a workload of 100 watts ( $p=0.009$ ) and significantly lower HR values (given as percent of the peak HR) at 50 and 100 watts ( $p=0.001$ ).

Cardiorespiratory fitness was inversely correlated with 2-h PG for the entire group ( $r=-0.237$ ) and in men ( $r=-0.404$ ). No significant correlations were found in women. Submaximal aerobic performance was not correlated with plasma glucose levels.

The 2-h PG level was inversely correlated with HDL cholesterol for the entire group ( $r=-0.372$ ,  $p<0.05$ ). In women, 2-h PG was inversely correlated with HDL cholesterol ( $r=-0.377$ ,  $p<0.05$ ), and FPG was positively

correlated with lnTG levels ( $r=0.458$ ,  $p<0.05$ ). No such correlations were found in men.

Table 2 shows the results of the backward regression analysis for the 2-h PG and FPG levels.

Age and cardiorespiratory fitness were significant predictors of 2-h PG levels in men. HDL was predictive in women.

lnTG levels predicted FPG levels in women, whereas BMI was the only predictor in men.

The symptom-limited incremental exercise test was stopped in 47 patients due to exhaustion, in 10 patients because of a BP greater than 240/120 mm Hg, in 4 patients because of arrhythmia and in 11 patients due to dyspnea.

## DISCUSSION

The main findings of the present analysis were that cardiorespiratory fitness was related to 2-h PG levels but not FPG levels, and this relationship was present in men only. Furthermore, we demonstrated that different risk factors predict 2-h PG and FPG levels in men and women. FPG levels were predicted by TG levels in women and BMI in men. Differences in 2-h PG were explained by cardiorespiratory fitness and age in men, whereas HDL was the only predictor in women.

The cardiorespiratory fitness findings are consistent with the Inter99 study in which high physical activity, as an indirect measurement of cardiorespiratory fitness, predicted a decline in 2-h PG levels in men only.<sup>14</sup> Furthermore, similar to the AusDiab study<sup>23</sup> and studies in Pima Indians,<sup>24</sup> 2-h PG levels were associated with the amount of physical activity, whereas FPG levels were not. Engberg et al. showed that physical activity was associated with a lower progression to diabetes in patients with isolated IGT but not in patients with isolated IFG.<sup>25</sup> It is suggested that the effect of physical activity on 2-h PG levels is mediated through an improvement in insulin sensitivity,<sup>26</sup> which in turn increases the insulin-stimulated glucose uptake after the glucose load.<sup>14</sup> Different pathogenic backgrounds of IFG and IGT<sup>16,17</sup> may explain these differences; stable reduced insulin secretion followed by a decline in primarily hepatic insulin sensitivity characterizes the transition from normal

**Table 2** - Summary of the stepwise regression with backward variable selection for the 2-h PG and FPG levels.

| Regression for 2-h PG levels |                        |                                 |                   |         |                                   |
|------------------------------|------------------------|---------------------------------|-------------------|---------|-----------------------------------|
| Gender                       | Variables in the Model | Regression coefficient (95% CI) | Standardized Beta | P Value | R <sup>2</sup> of the final Model |
| Men                          | Ppeak                  | -27.155<br>(-50.608/-3.702)     | -0.391            | 0.025   | 0.299                             |
|                              | age                    | -1.820<br>(-3.337/-0.303)       | -0.406            | 0.021   |                                   |
| Women                        | HDL                    | -1.105<br>(-1.843/-0.367)       | -0.457            | 0.004   | 0.209                             |
| Regression for FPG levels    |                        |                                 |                   |         |                                   |
| Gender                       | Variables in the Model | Regression coefficient (95% CI) | Standardized Beta | P Value | R <sup>2</sup> of the final Model |
| Men                          | BMI                    | 1.696<br>(0.369/3.023)          | 0.451             | 0.014   | 0.203                             |
| Women                        | lnTG                   | 6.932<br>(2.658/11.207)         | 0.486             | 0.002   | 0.236                             |

Variables included in the analysis were as follows: body mass index (BMI), age, blood pressure (BP), high-density lipoprotein cholesterol (HDL), ln transformed triglycerides (lnTG), and peak power output (Ppeak).

P- value for inclusion in the model was set at 0.1

glucose tolerance to IFG. In contrast, low whole-body insulin sensitivity with a secondary lack of beta-cell compensation is associated with the development of IGT.<sup>18</sup>

In studies with self-reported physical activity, which only correlates modestly with objective measures (i.e., exercise testing),<sup>13</sup> associations between sedentary habits and risk for type 2 diabetes may have been underestimated.<sup>10</sup> In the present investigation, cardiorespiratory fitness was objectively determined using a symptom-limited incremental cycle ergometry test. Cardiorespiratory fitness is considered an independent predictor of several cardiovascular diseases, diabetes mellitus and all-cause mortality.<sup>10,27</sup> The association between cardiorespiratory fitness and 2-h PG level may therefore explain why IGT but not IFG is considered a risk factor for cardiovascular disease.<sup>28,29</sup>

In women, differences in 2-h PG levels were explained by the differences in HDL levels. This finding is consistent with the findings of Njolstad et al., who showed that HDL cholesterol was inversely related to diabetes in women but not in men.<sup>30</sup> The differences in the HDL cholesterol effect based on gender may reflect sex hormone effects.<sup>31</sup> Furthermore, HDL subfractions and habitual alcohol intake disparities between men and women may play a role.<sup>31</sup>

In women, the only predictor for FPG was lnTG level. Accordingly, it has been shown that elevated TG levels are a more important risk factor for metabolic syndrome in women than in men.<sup>32</sup> Regitz-Zagrosek et al. concluded that risk factors for diabetes should be considered in a gender-specific manner that focuses on elevated TG levels in women and waist circumference in men.<sup>32</sup> The results of the present investigation may extend this conclusion by adding cardiorespiratory fitness for men and HDL cholesterol for women. From a practical perspective, increasing cardiovascular fitness is of major importance for men, whereas dietary interventions rather than physical activity to decrease body fat percentage are important measures for preventing type 2 diabetes in women. Similarly, Sui et al. showed that high levels of physical fitness did not eliminate the increased risk for diabetes in overweight and obese women.<sup>3</sup> However, cardiorespiratory fitness should not be ignored because it has been shown to be a significant predictor of all-cause mortality in women with IFG or undiagnosed diabetes.<sup>15</sup>

In the present investigation, men had lower submaximal performance parameters at fixed workloads (Table 1). However, this may be simply explained by the higher relative intensity in women.

Furthermore, women had a significantly higher diastolic blood pressure at rest than men because most of the women were more than 50 years old, and therefore have decreased circulating estrogen levels. Low estrogen levels independently contribute to an increase in blood pressure due to a direct effect on the arterial wall and the activation of both the renin-angiotensin system and the sympathetic nervous system.<sup>33,34</sup>

Some limitations of the present study must be addressed. This study is a cross-sectional analysis with a relatively small sample size. Due to the small sample size, we cannot entirely exclude a significant correlation between cardiorespiratory fitness and 2-h PG in women. However, our results do not provide any indication of such a relationship. Furthermore, we cannot rule out the possibility that variables that were removed by the stepwise algorithm of the regression might have some predictive capability.

Nonetheless, the results are essentially consistent with large cohort studies and add specific information on gender differences. Additional limitations include the following: the maximal cycle ergometry test was symptom limited, and gas analyses for the determination of maximal oxygen uptake values were not performed. Premature termination of the tests may have led to a slight underestimation of the peak power output in some cases. Although gas analysis is considered to be the gold standard for evaluating maximal oxygen uptake and would thus allow better comparison with other studies, the very close correlation between peak power output and maximal oxygen uptake ( $r=0.97$ )<sup>22</sup> justifies the decision to consider peak power output as an appropriate surrogate for maximal oxygen uptake. A further limitation is that we did not determine waist circumference.

## CONCLUSION

This study's findings suggest that high cardiorespiratory fitness is more beneficial in preventing the onset of diabetes in pre-diabetic men than in pre-diabetic women and that different risk factors predict 2-h PG levels and FPG levels in men compared to women. These findings may have important consequences for gender-specific diabetes prevention programs. Whereas increasing cardiorespiratory fitness should be a key goal for men, reducing body fat to improve the lipid profile is considered more beneficial in preventing type 2 diabetes in women. However, it must be emphasized that the present results do not negate the positive effects of increasing cardiorespiratory fitness in women.

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